Aortic Stenosis Background and Breakthroughs in Treatment: TAVR Update

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• As of 2017 I speak and proctor for
  – Abiomed
  – Medtronic
Aortic Stenosis- Overview

- Aortic Stenosis is a common finding in the elderly, and is associated with significant morbidity and mortality.
- The presenting symptoms are often referred to as the triad of symptoms:
  - Angina/ Dyspnea/ Syncope
- These are often the presenting symptoms of an inpatient hospitalization. Additionally, the finding of Aortic Stenosis may be a secondary or contributing factor to another reason for hospitalization.
- Once identified, expeditious evaluation and treatment is recommended.
Aortic Stenosis - Prevalence

- Prevalence of 12.4% in the >75 y/o population corresponds to 2.7 million people in North America.
- 540,000 are severe/symptomatic.
- 40% do not get SAVR.
- With expected increases in life expectancy, this will increase to 800,000 by 2025 and 1.4M by 2050.

From: Aortic Stenosis in the Elderly: Disease Prevalence and Number of Candidates for Transcatheter Aortic Valve Replacement: A Meta-Analysis and Modeling Study
Aortic Stenosis- nonreferral for AVR

Guidelines are not consistently followed. In actual practice, more than one third of patients eligible for AVR are not referred for evaluation. As the chart illustrates, five different surveys identified 33% to 60% of patients not referred for surgery. Additionally, the Euro Heart Survey of 5000 patients from 92 centers in 25 European countries determined that 32.3% of patients over the age of 75 were denied surgery.¹
Aortic Stenosis- reasons for nonreferral

Treatment decisions for older patients with severe AS are challenging due to comorbidity; they have a higher operative risk and have reduced life expectancy. In addition, their risk is increased by comorbidities such as heart disease and other conditions that are often present in this age group.
Valvular aortic stenosis is progressive and life-threatening. Once symptoms appear, untreated patients have a poor prognosis; they will experience worsening symptoms, eventually leading to death. After the onset of symptoms, average survival is 50% at two years and 20% at five years.²
Treatment of AS is effective
TAVR Genesis

- The first TAVR in man was performed in Rouen France in 2002 by Alain Cribier (Trained at Cedars Sinai)
- The first cases were actually done with a transseptal approach before the devices were modified for a retrograde aortic approach
- Cribier was instrumental in developing the Balloon Expandable Valves
- Self-Expanding Valves were developed contemporaneously
- To date worldwide there have been >200,000 TAVR implants
TAVR Genesis - Balloon Expandable vs Self Expanding:
The Partner Trial was the first RCT designed to establish the safety and efficacy of TAVR in comparison to Standard (Med Rx) and SAVR.

- Initiated in 2007
- Divided into two parts (Inoperable A, and High Surgical Risk B)
Partner A results: Inoperable Patients

TAVR vs Med Rx

* In an age and gender matched US population without comorbidities, the mortality at 5 years is 40.5%.

** Only 1 standard Rx patient was alive at 5 years who didn’t crossover to TAVR or had SAVR (out of protocol)
NYHA Class and Valve Performance

[Diagram showing NYHA Class and Valve Performance with graphs and data points for various time periods (Baseline, 1 Year, 3 Years, 5 Years).]
Partner B: High Risk Patients

All Patients (TF and TA)

Transfemoral Access Only
Partner B: High Risk Patients

SAVR: 40.6 Months
p (log rank) = 0.76

TAVR: 44.5 Months

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CoreValve was primarily a European Valve with CE Mark.

The US Pivotal Trial started later than Partner.

Randomization to Med Rx in Extreme Risk was no longer thought to be ethical.
CoreValve Pivotal Trial (TAVR vs SAVR)

**All-Cause Mortality**
- Transcatheter: 14.1%, 18.9%, 22.2%, 28.6%
- Surgical: 18.9%, 22.2%, 28.6%, 35.4%
- Log-rank $P=0.04$

**MACCE**
- Transcatheter: 16.5%, 20.7%, 24%, 27%
- Surgical: 20.5%, 23%, 25.7%, 29.7%
- Log-rank $P=0.01$
CoreValve Pivotal Trial

**All Stroke**

- Transcatheter
- Surgical

<table>
<thead>
<tr>
<th>Months Post-Procedure</th>
<th>0</th>
<th>6</th>
<th>12</th>
<th>18</th>
<th>24</th>
</tr>
</thead>
<tbody>
<tr>
<td>Transcatheter</td>
<td>391</td>
<td>364</td>
<td>335</td>
<td>318</td>
<td>205</td>
</tr>
<tr>
<td>Surgical</td>
<td>359</td>
<td>324</td>
<td>281</td>
<td>256</td>
<td>169</td>
</tr>
</tbody>
</table>

Log-rank P=0.05

\[ \Delta = 3.8 \]

\[ \Delta = 5.7 \]

\[ 12.5\% \]

\[ 8.7\% \]

\[ 16.6\% \]

\[ 10.9\% \]

**Other Clinical Endpoints**

<table>
<thead>
<tr>
<th>Events*</th>
<th>1 Month</th>
<th></th>
<th>1 Year</th>
<th></th>
<th>2 Years</th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>TAVR</td>
<td>SAVR</td>
<td>P</td>
<td>TAVR</td>
<td>SAVR</td>
<td>P</td>
</tr>
<tr>
<td>Vascular complications (major)</td>
<td>6.2</td>
<td>1.7</td>
<td>0.002</td>
<td>6.4</td>
<td>2.0</td>
<td>0.003</td>
</tr>
<tr>
<td>Pacemaker implant</td>
<td>20.0</td>
<td>7.1</td>
<td>&lt;0.001</td>
<td>22.5</td>
<td>11.6</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Bleeding (life threatening or disabling)</td>
<td>13.6</td>
<td>35.1</td>
<td>&lt;0.001</td>
<td>16.5</td>
<td>38.4</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>New onset or worsening atrial fibrillation</td>
<td>11.7</td>
<td>31.0</td>
<td>&lt;0.001</td>
<td>16.4</td>
<td>33.2</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Acute kidney injury</td>
<td>6.2</td>
<td>15.1</td>
<td>&lt;0.001</td>
<td>6.2</td>
<td>15.1</td>
<td>&lt;0.001</td>
</tr>
</tbody>
</table>

* Events included: Vascular complications (major), Pacemaker implant, Bleeding (life threatening or disabling), New onset or worsening atrial fibrillation, Acute kidney injury.
CoreValve Pivotal Trial

Paravalvular Regurgitation (Paired)

NYHA Class
Echocardiographic Findings

TAVR had significantly better valve performance over SAVR at all follow-up visits (P<0.001)
CoreValve Pivotal Trial
And now the bad news for SAVR...
TAVR- State of the Art (S3)

- TAVR devices have become smaller and more precise, allowing for better, more reliable and reproducible deployments, and reduced vascular complications.
- Notable on the Sapien 3 is the smaller sheath size (Expandable E-Sheath).
- Distal flexing of the catheter can allow for a more coaxial deployment.
- Fine tuning adjustments can now be made via a dial on the delivery catheter allowing for millimeter corrections.
- Additionally a “skirt” is used to reduce paravalvular leak.
The PARTNER II S3 Trial
Study Design

Symptomatic Severe Aortic Stenosis

ASSESSMENT by Heart Valve Team

Intermediate Risk Operable
(Pt S3i)

n = 1076 Patients

ASSESSMENT:
Optimal Valve Delivery Access

Transfemoral (TF)

TF TAVR
SAPIEN 3

Transapical/
Transaortic (TA/TAo)

TAA TAVR
SAPIEN 3

SAPIEN 3

2 Single Arm Non-Randomized
Historical-Controlled Studies

PII A
SAVR

PII A
SAPIEN

High Risk Operable/
Inoperable
(Pt S3HR)

n = 583 Patients

ASSESSMENT:
Optimal Valve Delivery Access

Transfemoral (TF)

TF TAVR
SAPIEN 3

Transapical/
Transaortic (TA/TAo)

TAA TAVR
SAPIEN 3
TAVR State of the Art: S3

Mortality and Stroke: S3HR
At 30 Days (As Treated Patients)

Mortality
- All-Cause
- Cardiovascular

Stroke
- All Stroke
- Disabling

O:E = 0.26
(STS 8.6%)

S3HR

Mortality and Stroke: S3i
At 30 Days (As Treated Patients)

Mortality
- All-Cause
- Cardiovascular

Stroke
- All Stroke
- Disabling

O:E = 0.21
(STS 5.3%)

S3i
TAVR State of the Art: S3

Mortality: S3HR & S3I
At 30 Days (As Treated Patients)

<table>
<thead>
<tr>
<th>Transfemoral</th>
<th>Transapical / Transaortic</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-Cause</td>
<td>Cardiovascular</td>
</tr>
<tr>
<td>All-Cause</td>
<td>Cardiovascular</td>
</tr>
</tbody>
</table>

- Transfemoral:
  - S3HR: 491, 1.6%
  - S3I: 947, 1.1%

- Transapical / Transaortic:
  - S3HR: 92, 5.4%
  - S3I: 125, 3.3%

Other Clinical Events
At 30 Days (As Treated Patients)

<table>
<thead>
<tr>
<th>Events (%)</th>
<th>S3HR Overall (n=583)</th>
<th>S3HR TF (n=491)</th>
<th>S3HR TA/T Ao (n=92)</th>
<th>S3I Overall (n=1076)</th>
<th>S3I TF (n=951)</th>
<th>S3I TA/T Ao (n=125)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Major Vascular Complications</td>
<td>5.0</td>
<td>5.3</td>
<td>3.3</td>
<td>5.6</td>
<td>5.9</td>
<td>3.2</td>
</tr>
<tr>
<td>Bleeding - Life Threatening</td>
<td>6.3</td>
<td>5.5</td>
<td>10.9</td>
<td>5.4</td>
<td>4.4</td>
<td>12.9</td>
</tr>
<tr>
<td>Annular Rupture</td>
<td>0.3</td>
<td>0.2</td>
<td>1.1</td>
<td>0.2</td>
<td>0.2</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial Infarctions</td>
<td>0.5</td>
<td>0.4</td>
<td>1.1</td>
<td>0.3</td>
<td>0.3</td>
<td>0</td>
</tr>
<tr>
<td>Coronary Obstruction</td>
<td>0.2</td>
<td>0.0</td>
<td>1.1</td>
<td>0.4</td>
<td>0.4</td>
<td>0</td>
</tr>
<tr>
<td>Acute Kidney Injury</td>
<td>1.0</td>
<td>0.8</td>
<td>2.2</td>
<td>0.5</td>
<td>0.3</td>
<td>1.6</td>
</tr>
<tr>
<td>New Permanent Pacemaker</td>
<td>13.0</td>
<td>13.2</td>
<td>12.0</td>
<td>10.1</td>
<td>10.4</td>
<td>7.2</td>
</tr>
<tr>
<td>Aortic Valve Re-Intervention</td>
<td>1.0</td>
<td>0.8</td>
<td>2.2</td>
<td>0.7</td>
<td>0.8</td>
<td>0</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>0.2</td>
<td>0.2</td>
<td>0</td>
<td>0.1</td>
<td>0.1</td>
<td>0</td>
</tr>
</tbody>
</table>

DaVita | HealthCare Partners.
TAVR- State of the Art (Evolute)

- Lower profile (14 fr)
- Recapturable/Repositionable (at up to 80% deployment)
- Reduced PPM
- Reduced Paravalvular Leak
Evolute CE Mark Study

**EVOLUT CE Mark: Purpose**

The CoreValve Evolut R CE Clinical Study was designed to assess the safety and clinical performance of the CoreValve Evolut R System (26 mm, 29 mm) in symptomatic extreme- or high-risk patients with aortic stenosis (Heart Team assessment) enrolled at 6 centres in Australia, the United Kingdom, and New Zealand.

**Evolut CE Mark: Baseline Demographics**

<table>
<thead>
<tr>
<th>Characteristic</th>
<th>N=60</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>82.8 ± 6.1</td>
</tr>
<tr>
<td>Women</td>
<td>66.7</td>
</tr>
<tr>
<td>Body surface area (m²)</td>
<td>1.7 ± 0.2</td>
</tr>
<tr>
<td>STS Predicted Risk of Mortality (%)</td>
<td>7.0 ± 3.7</td>
</tr>
<tr>
<td>Logistic EuroSCORE I (%)</td>
<td>20.5 ± 12.5</td>
</tr>
<tr>
<td>New York Heart Association class III or IV</td>
<td>68.3</td>
</tr>
<tr>
<td>Previous CABG</td>
<td>28.3</td>
</tr>
<tr>
<td>Any chronic lung disease</td>
<td>43.3</td>
</tr>
<tr>
<td>Diabetes</td>
<td>26.7</td>
</tr>
<tr>
<td>Peripheral vascular disease</td>
<td>16.7</td>
</tr>
<tr>
<td>Atrial fibrillation / atrial flutter</td>
<td>36.7</td>
</tr>
<tr>
<td>Frailty</td>
<td>68.3</td>
</tr>
<tr>
<td>Pre-existing permanent pacemaker</td>
<td>11.7</td>
</tr>
</tbody>
</table>

Meredith I EuroPCR 2015
# TAVR - State of the Art (Evolute)

## Evolut CE Mark: Safety

<table>
<thead>
<tr>
<th>Event, K-M rates (no. of patients)</th>
<th>30 Days N=60</th>
<th>6 Months N=60</th>
</tr>
</thead>
<tbody>
<tr>
<td>All-cause mortality</td>
<td>0.0 (0)</td>
<td>5.0 (3)</td>
</tr>
<tr>
<td>Cardiovascular</td>
<td>0.0 (0)</td>
<td>3.3 (2)</td>
</tr>
<tr>
<td>All stroke</td>
<td>0.0 (0)</td>
<td>1.7 (1)</td>
</tr>
<tr>
<td>Disabling</td>
<td>0.0 (0)</td>
<td>1.7 (1)</td>
</tr>
<tr>
<td>Non-disabling</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
</tr>
<tr>
<td>Major vascular complications</td>
<td>8.3 (5)</td>
<td>8.3 (5)</td>
</tr>
<tr>
<td>Life-threatening or disabling bleeds</td>
<td>5.0 (3)</td>
<td>8.4 (5)</td>
</tr>
<tr>
<td>Embolization or migration</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
</tr>
<tr>
<td>Endocarditis</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
</tr>
<tr>
<td>Coronary obstruction</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
</tr>
<tr>
<td>Valve thrombosis</td>
<td>0.0 (0)</td>
<td>0.0 (0)</td>
</tr>
<tr>
<td>Pacemaker*</td>
<td>11.7 (7)</td>
<td>13.4 (8)</td>
</tr>
</tbody>
</table>

*Patients with a prior pacemaker included in the denominator.

## Evolut CE Mark: NYHA Class

Compared with Baseline, 74.9% Improved at 30 Days and 84.9% at 6 Months

- **Baseline N=60**
  - NYHA I: 60.0%
  - NYHA II: 31.7%
  - NYHA III: 8.3%
  - NYHA IV: 11.3%

- **30 Days N=59**
  - NYHA I: 50.8%
  - NYHA II: 37.3%
  - NYHA III: 11.9%

- **6 Months N=53**
  - NYHA I: 67.9%
  - NYHA II: 44.1%
  - NYHA III: 11.3%
  - NYHA IV: 20.8%
TAVR - State of the Art (Evolute)
AS Case 1

- 74 y/o with Progressive SOB/Edema.
- Hx CAD/ CABG/ PPM
- Cirrhosis/ COPD with active EtOH and Tob
AS Case 1
AS Case 1
AS Case 1
AS Case 1
AS Case 1
AS Case 2

• 76 y/o woman with progressive dyspnea and Edema.
• Hx of Pulmonary HTN.
• Colon Ca dx within the past year.
• On Intermittent Chemotherapy.
AS Case 2
AS Case 2
AS Case 2
AS Case 2
• 84 y/o gentleman with a 12 yr old bioprosthetic valve initially placed for Severe Aortic Stenosis.
• 23 mm Edwards Perimount Valve
• Class 3-4 NYHA class
• EF 35% (dropping)
• Frail (poor candidate for redo sternotomy)
• Large ascending thoracic aorta
Bioprosthetic Valve Degeneration

AORTIC ROOT

Aortic Root Angle

ANNULUS

SINUS HEIGHT

LCC

RCC

NCC
Bioprosthetic Valve Degeneration
Bioprosthetic Valve Degeneration
AS Case 3

• 79 y/o with severe back pain/ radiculopathy with spinal stenosis.
• Needed urgent back surgery. Found to have Severe AS by echo.

• Mild CAD by Cath
• BAV was done with gradient dropping from 40 mmHg to 20 mmHg and AVA increased from 0.7 to 1.0.
• Pt had uneventful surgery and was brought back for TAVR
AS Case 3
AS Case 3
Thank You

Evolution of structural interventions

1. Surgery is the only treatment
2. Surgery is the gold standard treatment
3. Surgery is the preferred treatment for low and intermediate risk patients
4. Transcatheter interventions are performed in intermediate risk patients
5. Surgery is performed in patients with contraindication to transcatheter approach